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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,122	12/14/2001	Jeanette McCarthy	MMI-007	9042

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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,122	MCCARTHY, JEANETTE	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-130* is/are pending in the application.

4a) Of the above claim(s) *31-40 and 58-130* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30 and 41-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *0903* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed May 12, 2003. Currently, claims 1-130 are pending. Claims 31-40, 58-130 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election without traverse of Group I, claims 1-30, 41-57 in the paper filed is acknowledged.

Priority

3. This application claims priority to provisional application 60/327,487, filed October 9, 2001.

Drawings

4. The drawings are acceptable.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 41, 43-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to "the F7 genetic profile", "polymorphic region of the F7 gene," "F7 allelic variants."

The specification teaches identifying polymorphisms at residue 594 of the reference sequence GI 180333 (Genbank Accession Number J02933, November 1994). The polymorphism has been designated F7u1 which is a silent variant. The second polymorphism identified is a change from a C to a T in the F7 gene at residue 8401 which is a non-coding variant (page 3, lines 9-15). Moreover, the specification identifies a SNP, namely F7u9 which "has been previously associated with vascular disease."

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA…' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a

mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Applicant has defined only three polymorphic variants with the F7 gene. As provided in Example 11 of the Written Description Guidelines directed to "allelic variants," there is no description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO: 1 relates to the structure of any strictly neutral alleles. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes of the genus are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only three members of this genus is not representative of the variants of the genus and is insufficient to support the claims.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-30, 41-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of aiding in the diagnosis of

myocardial infarction or coronary artery disease by detecting the presence of two copies of a thymidine allele at position 8401 of SEQ ID NO: 1 as indicative of increased likelihood of myocardial infarction or coronary artery disease, does not reasonably provide enablement for methods of treatment based upon the presence of polymorphisms, methods of determining predisposition based upon the presence of 594 of SEQ ID NO: 1 . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-30, 41-57 are directed to methods of detecting polymorphisms within the F7 gene which are indicative of a predisposition to developing vascular disease.

The invention is in class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Teachings of the Specification and the presence of Working Examples

The specification teaches identifying polymorphisms at residue 594 of the reference sequence GI 180333 (Genbank Accession Number J02933, November 1994). The polymorphism has been designated F7u1 which is a silent variant. The second polymorphism identified is a change from a C to a T in the F7 gene at residue 8401 which is a non-coding variant (page 3, lines 9-15). Moreover, the specification identifies a SNP, namely F7u9 which "has been previously associated with vascular disease."

The specification asserts that the two newly discovered polymorphisms, namely F7u1 and F7d10 are in linkage disequilibrium with F7u9 and "F7u1 and F7d10 SNPs at as markers for the F7u9 SNP and can thus be used to predict risk of vascular disease, e.g., CAD and MI" (page 3, lines 17-21). The specification analyzed a population of individuals to determine that two copies of a T at nucleotide 8401 are at increased risk for vascular disease (lines 22-26). The specification demonstrates that the F7u9 and F7u1 and F7d10 SNPs are in linkage disequilibrium with each other at a p-value of 0.0001 (page 11, lines 20-24).

The specification states that F7u9 was previously associated with vascular disease. The support in the specification states that "some investigators have found that individuals who have either one or two copies of the A allele are at decreased risk of MI while other investigators have found carriers of the A allele to be at increased risk of MI (page 11, lines 15-23). This passage in the specification illustrates that it is unpredictable whether the F7u9 mutation is associated with vascular disease, and as such could not be used to enable the newly discovered mutations.

The specification has working examples directed to a case-control population. 352 Caucasian subjects with premature coronary artery disease were identified in medical centers with either myocardial infarction, surgical or percutaneous

revascularization or a significant coronary artery lesion. The controls were a random sample of 418 Caucasians from Georgia (page 82). As seen in Table 2, the genotypes are analyzed against controls, CAD cases and MI cases. Approximately 1% of control individuals compared to approximately 4% of CAD and MI cases had a genotype at polymorphism F7d10 of a TT (page 84).

The unpredictability of the art and the state of the prior art

There is a great deal of unpredictability in the association of mutations with particular diseases. As clearly evidenced by the teachings in the specification "some investigators have found that individuals who have either one or two copies of the A allele are at decreased risk of MI while other investigators have found carriers of the A allele to be at increased risk of MI (page 11, lines 15-23). Thus, depending on a sample size, ethnicity, and other factors, an association may not be determined.

The prior art provides the human blood coagulation factor VII gene (Genbank Accession Number J02933, November 1994).

Although the instant specification appears to indicate the F7u9 was previously known in the art to be associated with vascular disease, the examiner was unable to locate any references or citations to this effect. The examiner contacted the applicant on August 28, 2003 to obtain further information regarding the location of art for this assertion, however, the applicant did not provide the information.

Moreover, prior to the filing of the instant application, GenSeq Accession Number AAC71304 and AAC71295 each teach a single nucleotide polymorphism, namely C8401T (F7d10) and G594A (G7d10) (see WO 00/58519 with alignments attached). The polymorphisms are disclosed to be used to diagnose a laundry list of diseases,

however, provides not specific examples or correlation. Thus the art teaches the presence of the "new" polymorphisms prior to the filing date.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this association to individuals given the negative teachings of association in the art.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Guidance in the Specification.

The teachings of the specification do not establish that one could actually detect a polymorphism at 594 and 8401 of SEQ ID NO: as an indicator of vascular disease. Rather the teachings of the specification asserts that the polymorphism at 8401 of SEQ ID NO is present in both control and vascular disease individuals.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. While one could conduct additional experimentation to determine whether, e.g., the polymorphism at 594 and 8401 of SEQ ID NO might be associated with e.g., vascular disease, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue.

Turning to the claimed invention, the claims are drawn to various embodiments of identifying subjects as candidates for further course of action following the determination of the presence of the polymorphisms. First, as discussed above, using the 594 and 8401 polymorphisms as indicators of vascular disease based upon their linkage disequilibrium with a previously associated polymorphism is not enabled. Weighing the evidence on the record, there is insufficient evidence to illustrate that the

F7u9 polymorphism is associated with vascular disease since the specification clearly illustrates that more than one group of investigators disagrees about the association of the F7u9 polymorphism and vascular disease. As noted above, the examiner was unable to analyze the association because the investigators and/or their work was not identified in the specification, was not provided by applicants following a request by the examiner and were not readily found by the examiner.

Second, the specification fails to provide any analysis with respect to the 594 polymorphism and the frequency in diseased and control populations. Thus, it is unpredictable that the polymorphisms is associated with vascular disease and the extent to which the association exists.

Finally, with respect to the 8401 polymorphism, the information provided in Table 2 appears to illustrate an increased risk for CAD and MI for individuals with homozygosity for TT. However, vascular disease is a very broad category of diseases which encompasses not only coronary artery disease (CAD) and myocardial infarction but also diseases such as peripheral vascular disease, collagen vascular diseases (rheumatoid arthritis, systemic lupus erthematosus, scleroderma, dermatomyositis, polyarteriris nodosa, for example), ischemia, stroke, venous thromboembolism and pulmonary embolism, for example (see Claim 51 or 55). This is a very large group of diseases which have not been analyzed and do not have the same genetic foundation. The modes of inheritance and genetic predisposition to each of these diseases has not been thoroughly elucidated by either the art or the specification to enable the skilled artisan to apply an association of one disease with all other vascular diseases without further undue experimentation.

More specifically, many of the claims are directed to identifying subjects for surgical procedures or other very invasive and life threatening procedures. Invasive and non-

invasive further analysis using CT, ultrasounds are distinguishable with respect to the pending claims. For the claims drawn to further imaging and procedures which, while costly, would be plausible, however, procedures such as surgery, implantation of pacemakers, implantation of a defibrillator, implantation of stents or bypass grafting have not been enabled for the skilled artisan to use. The claims and the specification are suggesting that based upon the presence of a single polymorphism, a subject should be selected for a clinical course of therapy which includes very invasive and risky procedures. The treatments based upon a polymorphism, without further analysis which indicates additional risk factors, is extreme. For example, an individual which is positive for the polymorphisms identified in the instant application, may have healthy arteries. Performing a surgery such as implantation of a stent, defribillator or pacemaker or a bypass graft would be without merit. If a surgeon were to enter an individual to perform one of these procedures, without a blockage, he would be unable to perform the intended method. Moreover, the risk of complications due to surgery weighs heavily in performing additional experiments prior to surgical procedures. Thus, to the extent that the claims are directed to detecting a polymorphism in an individual and identifying the subject for surgical procedures, the skilled artisan would be required to perform more experimentation.

With respect to Claims 41-44, the claims are drawn to methods for diagnosing or aiding in the diagnosis of vascular disease or disorder by determining the genetic profile of the subject, the claims are not limited to the two polymorphism newly discovered in the specification. The specification has not provided what is encompassed by "the F7 genetic profile." Moreover, as noted above, neither the F7u1 or F7u9 polymorphisms have been associated with vascular diseases.

With respect to Claims 45-47, the claims are drawn to a method of selecting the appropriate drug to administer to a subject, however the instant specification has provided no particular analysis with respect to either of new polymorphisms and appropriate drugs for a subject. The claims are not limited to the instant polymorphisms, therefore, the claims broadly encompass polymorphisms which are not disclosed in the instant specification and their affect on appropriateness of drugs. The skilled artisan would be required to perform significant analysis to determine how polymorphisms affect any drug which may be administered to an individual at risk for vascular disease.

With respect to Claims 48-49, the claims are drawn to administering to the subject a compound that modulates F7 gene expression or protein activity. The instant specification has not associated F7 allelic variants with vascular diseases, nor any disease or condition, as encompassed by the instant claims. Moreover, the specification has not provided any demonstration that administrating a compound will be effective to modulate F7 gene expression or protein activity. A skilled artisan would be required to perform additional experimentation to determine whether specific compounds would modulate F7 expression.

In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of the claimed invention. However, the closest prior art does not provide support for the use of polymorphism at 8401 of SEQ ID NO 1 as an indicator for vascular disease.

Thus, it is unpredictable as to whether one could successfully use the claimed invention, and given the fact that neither the specification nor the prior art provide evidence of a correlation or association between the polymorphism at 594 and 8401 of SEQ ID NO 1 and vascular disease, it is further unpredictable as to whether any

quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention. In light of the teachings in the prior art, and the general unpredictability concerning the association between polymorphism at 594 and 8401 of SEQ ID NO 1 and vascular disease, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the presence of a possible association between the 594 and 8401 polymorphisms and vascular disease, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the lack of association between the polymorphism and the mutation. Thus given the claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define an association for screening a subject, the lack of guidance provided in the specification, and the absence of a working examples providing an association balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 41-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 41-44 are indefinite over the recitation "the F7 genetic profile" because "the F7 genetic profile" lacks proper antecedent basis. The claims does not refer to a genetic profile and is unclear what is intended. Thus, the metes and bounds of the claimed invention are unclear.

B) Claims 45-47 are indefinite because it is unclear whether the claims are limited to methods of selecting appropriate drug to administer or the claims are intended to be limited determining the molecular structure of at least a portion of an F7 gene. The claims are drawn to methods of selecting appropriate drug to administer however, the final step is one of determining the molecular structure of at least a portion of an F7 gene. Accordingly, it is unclear as to whether the claimed method is one for selecting appropriate drug to administer or the claims or determining the molecular structure of at least a portion of an F7 gene.

C) Clams 48-49 are because it is unclear whether the claims are limited to methods of treating a subject having a disease or the claims are intended to be limited to administering a compound which modulates the F7 gene expression or protein activity. The claims are drawn to methods of treating a subject having a disease however, the final step is one of administering a compound which modulates the F7 gene expression or protein activity. It is noted that administering to the subject a compound does not imply that the compound treats a subject for a disease.

Accordingly, it is unclear as to whether the claimed method is one for treating a subject having a disease or the claims or administering a compound which modulates the F7 gene expression or protein activity.

D) Claims 50-57 are indefinite over the recitation determining the identity of the nucleotides at positions 594 and/or 8401 because the final process step is directed to indicating the increased likelihood of a vascular disease by detecting TT at position 8401. However, as written, the claims are directed to embodiments which sample only 594. The claims provide no guidance as to how to use the information in the likelihood or diagnosis of vascular disease. Thus, to the extent that the claim reads upon the polymorphism at position 594, the metes and bounds of the claimed invention are unclear.

Conclusion

8. No claims allowable.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
Patent Examiner
September 5, 2003